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Tris(4-chlorophenyl)methane (TCPMe) and Tris(4-chlorophenyl)methanol (TCPMOH) Research Concept

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TCPMe and TCPMOH Nomination

Nominated by NIEHS for toxicological characterization

- Apparent widespread occurrence and persistence in the environment
- Limited availability of toxicity data
- Found in human tissues
  - Presumed to be bioaccumulative
- TCPMOH is a potent competitive inhibitor of human and rodent androgen receptors *in vitro*
- Need to characterize potential human health hazard relative to other endocrine active agents

TCPMe and TCPMOH Background

- Use and Production
  - TCPMe is a by-product in the production of DDT
  - TCPMOH is a presumed metabolite of TCPMe
  - Some industrial uses reported but no production data located
- Human Exposure
  - Primary human exposure presumed to be from consumption of food
  - Human adipose, liver, bile, breast milk (not U.S.)
    - High end: TCPMe ~70 ng/g; TCPMOH ~38 ng/g lipid
  - Bioaccumulates in marine food web
    - Marine mammal blubber levels > 1 μg/g lipid

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TCPMe and TCPMOH Structures

QuickTime™ and a
TIFF (Uncompressed) decompressor
are needed to see this picture.

TCPMe

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TCPMOH

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p,p'-DDT

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Dicofol

TCPMOH Toxicity

- 28 day oral study in rats
  - Changes in liver, spleen, blood counts at ~10 mg/kg
- Endocrine activity *in vitro*
  - Altered human sperm motility, vitality, acrosome reaction
  - Binding/antagonism at rat and human androgen receptors
  - Conflicting data on activity against human estrogen receptor
- Endocrine activity *in vivo*
  - 28 day oral study in sexually mature male rats
    - Increased serum FSH, no effect on serum LH or testosterone
    - No effect on testicular morphology or occurrence of apoptotic figures
- No information on ADME, genotoxicity, immune, developmental, reproductive toxicity

Proposed Approach

Tier 1

- ADME studies
  - Single and multiple oral exposures
  - Blood and tissue levels, metabolite identification
- Endocrine modulation studies (androgen and estrogen receptors)
  - *In vitro*, *in vivo* (confirmatory)
- Genotoxicity studies

Tier 2

- Subchronic toxicity studies, *in utero* / perinatal exposure
  - Immune, developmental, reproductive evaluations in F1

Tier 3

- Multigeneration reproductive toxicity studies
- Carcinogenicity studies

Questions and Comments